Express Mail No. **EV 335 858 251 US**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of:	Burchard	Confirmation No.:	6450
Serial No.:	09/616,849	Art Unit:	1634
Filed:	July 14, 2000	Examiner:	Forman, Betty J.
For:	METHOD FOR DETERMINING THE SPECIFICITY AND SENSITIVITY OF OLIGONUCLEOTIDES FOR HYBRIDIZATION	Attorney Docket No:	9301-044

BRIEF ON APPEAL FEE TRANSMITTAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

An original and two copies of the applicant's Brief on Appeal in the above-entitled application are submitted herewith. The item(s) checked below apply:

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The brief filing fee is:

- ☒ Required.
- ☐ Not required. (Fee paid in prior appeal.)

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Respectfully submitted,

Date: January 6, 2004

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Enclosure

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BRIEF ON APPEAL

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TABLE OF AUTHORITIES

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
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Serial No.: 09/616,849

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For: METHOD FOR DETERMINING THE SPECIFICITY AND SENSITIVITY OF OLIGONUCLEOTIDES FOR HYBRIDIZATION

Confirmation No.: 6450

Art Unit: 1634

Examiner: Forman, Betty J.

Attorney Docket No: 9301-044

BRIEF ON APPEAL UNDER 37 C.F.R. §§ 1.191 AND 1.192

Mail Stop Appeal Brief-Patents
Commissioner for Patents
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Alexandria, VA 22313-1450

Sir:

This is an appeal under 35 U.S.C. § 134 from a final rejection mailed April 7, 2003 of claims 27-30, 33-40, 42-54, 59-68, 73-75, 84-85 and 90-104 of the above-identified application. The Notice of Appeal was filed on August 7, 2003. Appellant submits this appeal brief in triplicate, accompanied by (1) a Petition for Extension of Time (in duplicate) for three months from October 7, 2003 up to and including January 7, 2004, accompanied by the appropriate fee; and (2) a Brief on Appeal Fee Transmittal Sheet.

I. REAL PARTY IN INTEREST

Rosetta Inpharmatics LLC is the assignee of this application, and the real party in interest. An assignment transferring the right, title, and interest of inventor Julja Burchard to Rosetta Inpharmatics, Inc. was submitted for recordation with the U.S. Patent and Trademark Office on July 14, 2000 and recorded on Reel 010993 at Frame 0334. An assignment transferring the right, title, and interest of Rosetta Inpharmatics, Inc. to Rosetta Inpharmatics LLC was submitted for recordation with the U.S. Patent and Trademark Office on November 20, 2003.

II. RELATED APPEALS AND INTERFERENCES

Appellant is not aware of any other appeals or interferences which will directly affect, or be directly affected by, or having a bearing on the Board's decision in the present appeal.

III. STATUS OF THE CLAIMS

Claims 27-30, 33-40, 42-54, 59-68, 73-75, 84, 85, and 90-104 are rejected[1].

Claims 1-26, 31, 32, 41, 55-58, 69-72, 76-83 and 86-89 have been canceled.

Claims 27-30, 33-40, 42-54, 59-68, 73-75, 84-85 and 90-104 are appealed.

IV. STATUS OF AMENDMENTS

All amendments have been entered. Appellant did not file any claim amendments subsequent to the final rejection dated April 7, 2003.

V. SUMMARY OF THE INVENTION

The presently claimed invention relates to a method for evaluating a binding property of a polynucleotide probe comprising a predetermined nucleotide sequence to a target nucleotide sequence (see the instant specification at page 3, line 35 through page 4, line 3 and page 5, lines 22-32). The method comprises determining a ratio of the amount of hybridization of polynucleotides in a first sample to the polynucleotide probe and the amount of hybridization of polynucleotides in a second sample to the polynucleotide probe (see page 40, line 30, through page 41, line 36; and page 48, line 28, through page 49, line 11). The ratio is used as a measure of the binding property (see page 40, line 30, through page 41, line 36). The first sample is a "specific" hybridization sample in which a substantial portion of the polynucleotide molecules are polynucleotide molecules

[1] In the Advisory Action mailed September 8, 2003, the Examiner has indicated that only claims 27-30, 33-36, 44-47, 59-68, 73-75, 90, 91 and 93 are rejected (Advisory Action, item 7). Pursuant to a telephone conversation between Appellant's representative Weining Wang and Examiner Betty Forman on November 25, 2003, claims 37-40, 42, 43, 48-54, 84, 85, 90, 92 and 94-104 are also rejected but were inadvertently omitted from the Advisory Action. Thus, all pending claims, i.e., claims 27-30, 33-40, 42-54, 59-68, 73-75, 84, 85, and 90-104, are rejected.

comprising the target nucleotide sequence (*e.g.*, at least 75% pure of polynucleotide molecules comprising the target nucleotide sequence), whereas the second sample is a "non-specific" hybridization sample which comprises a plurality of different polynucleotide molecules having different polynucleotide sequences (see, e.g., the instant specification at page 6, line 13, through page 7, line 17 and page 7, lines 27-33).

The first sample is a sample which is at least 75% pure, at least 90% pure, at least 95% pure, or at least 99% pure in polynucleotide molecules comprising the target nucleotide sequence (see, e.g., the instant specification at page 6, lines 33-37).

The second sample can be a sample comprising nucleotide sequences of a plurality of genes or gene transcripts of a cell or organism (see, e.g., the instant specification at page 6, lines 23-30 and page 7, lines 2-5). The second sample can also be a sample that does not comprise the target sequence, i.e., each different polynucleotide molecule in the second sample does not comprise the target nucleotide sequence, e.g., a polynucleotide sample from a deletion mutant of the cell or organism, where the deletion mutant of the cell or organism does not express the target gene or gene transcript (see, e.g., the instant specification at page 6, lines 23-30 and page 7, lines 2-5 and lines 11-17). The second sample can also be a sample that comprises the target sequence as well as other non-target sequences, e.g., a polynucleotide sample from a wild-type strain of the cell or organism, wherein the wild-type strain of the cell or organism expresses the target gene or gene transcript (see, e.g., the instant specification at page 7, lines 11-17).

In specific embodiments of the claimed invention, the first sample further comprises polynucleotide molecules that do not comprise the target nucleotide sequence, and the second sample comprises: (i) polynucleotide molecules comprising the target nucleotide sequence, and (ii) a plurality of different polynucleotide molecules, each different polynucleotide molecule comprising a different nucleotide sequence and not comprising the target nucleotide sequence (see, e.g., the instant specification at page 9, line 17 through page 10, line 5; and page 33, lines 20-25). In one embodiment, the amount of polynucleotide molecules in the first sample comprising the target nucleotide sequence differs from the amount of polynucleotide molecules in the second sample comprising the target nucleotide sequence by at least a factor of two, at least a factor of four, at least a factor of eight, at least a factor of twenty, or at least a factor of 100 (see, e.g., the instant

specification at page 33, lines 28-21). In another embodiment, each polynucleotide molecule that does not comprise the target nucleotide sequence in the first sample is present in the second sample in an amount that differs from the amount of said polynucleotide molecule in the first sample by no more than a factor of 100, no more than a factor of 10, no more than 50% (see, e.g., the instant specification at page 34, lines 2-6). In still another embodiment, the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than a factor of two, no more than 50%, no more than 10%, no more than 1% (see, e.g., the instant specification at page 34, lines 12-15).

The invention also relates to a method for evaluating a binding property of a plurality of polynucleotide probes to a target nucleotide sequence (see, e.g., the instant specification at page 10, lines 7-9). The method comprises determining a ratio of the amount of hybridization of polynucleotides in a first sample to each polynucleotide probe in the plurality of polynucleotide probes and the amount of hybridization of polynucleotides in a second sample to each polynucleotide probe in the plurality of polynucleotide probes. The first and second samples can be those described above in connection with the method for evaluating a binding property of a probe (see, e.g., the instant specification at page 10, lines 9-15).

VI. ISSUES

The following issues are presented for review in this appeal:

Firstly, whether claims 27-30, 33-36, 44-47, 59-68, 73-75, 90, 91 and 93 are obvious under 35 U.S.C §103(a) over Lockhart et al., U.S. Patent No. 6,344,316 B1 ("Lockhart") in view of Bao et al., U.S. Patent No. 6,251,601 ("Bao").

Secondly, whether claims 37-40, 42, 43, 48-54, 84, 85, 90, 92 and 94-104 are obvious under 35 U.S.C §103(a) over Lockhart in view of Bao as applied to claims 27, 67, 91 and 93 and further in view of Brown et al., U.S. Patent No. 5,807,522 ("Brown").

VII. GROUPING OF CLAIMS

The rejected claims do not stand or fall together. Appellant considers claims 40, 42-54, 90 (to the extent claim 90 depends on claims 40 and 42-54), and 91-104 to be separately patentable from claims 27-30, 33-39, 59-68, 73-75, 84-85, and 90 (in part). The reasons why claims 40, 42-54, 90 (in part), and 91-104 are separately patentable are presented in Section D of the Argument.

VIII. ARGUMENT

A. The References

Lockhart teaches methods for identifying differences in nucleic acid abundances (e.g., expression levels) between two or more samples using high density DNA microarrays. In Lockhart, a method of optimizing a set of probes for detection of a particular gene is disclosed. The probe optimization method involves first hybridizing the probes with their target nucleic acids alone and then hybridizing the probes with a high complexity, high concentration nucleic acid sample that does not contain the targets complementary to the probes (Lockhart, column 36, lines 30-36), and selecting those probes that show a strong hybridization signal with their target and little or no cross-hybridization with the high complexity sample as preferred probes for use in the high density arrays (Lockhart, column 36, lines 44-47). For selection of probes showing a strong hybridization signal with their target, Lockhart teaches that the probes are hybridized to a sample containing target nucleic acids having subsequences complementary to the oligonucleotide probes, and those probes are selected for which the difference in hybridization intensity between the probes and their respective mismatch controls exceeds a threshold hybridization intensity (see, e.g., Lockhart col. 37, lines 1-12). For selection of probes showing little or no cross-hybridization, Lockhart teaches that the probes can be hybridized with a nucleic acid sample that is not expected to contain sequences complementary to the probes, and those probes are selected for which both the probes and their mismatch controls show hybridization intensities below a threshold value (see, e.g., Lockhart col. 37, lines 13-27). Thus, in Lockhart, selection of probes that show a strong hybridization signal with their target and little or no cross-hybridization is achieved by evaluating a probe according to its ability to hybridize to the target sample, and comparing this ability to a threshold, and separately, evaluating the probe according to its ability to hybridize to the non-target sample, and comparing this latter

ability to a threshold. Lockhart does not teach or suggest comparing directly the hybridization signal and cross-hybridization signal of the same probe, much less combining the hybridization signal and cross-hybridization signal of the same probe into a single quantity, e.g., a ratio, and using such a single quantity as a measure of the binding property of the probe.

Bao teaches a multi-color, comparative hybridization assay using an array of nucleic acid target elements attached to a solid support for the simultaneous detection of both gene expression and chromosomal abnormalities in a tissue sample. The method of Bao employs a comparative hybridization of a tissue mRNA or cDNA sample labeled with a first marker (e.g., a first fluorescent color), a tissue chromosomal DNA sample labeled with a second marker (e.g., a second fluorescent color), and at least one reference nucleic acid labeled with a third marker (e.g., a third fluorescent color), to the array (see Bao, Abstract). Bao teaches detecting the fluorescent color presence and intensity at each of at least two target elements, and determining the fluorescent ratios (i) of the first and third colors and (ii) the second and third colors (see Bao, Abstract). Bao teaches comparing the fluorescence data at each target element to produce the ratio between any desired tissue and reference or between tissues (see, Bao, column 16, lines 36-38). Bao also teaches image analysis and processing (see, Bao, column 16, line 45, through column 17, line 62). For example, Bao teaches determining the ratio of background corrected tissue intensity over background corrected reference intensity B/D or C/D, where B is tissue DNA intensity, C is tissue cDNA intensity, and D is reference intensity (see, Bao, column 17, lines 20-37). Bao does not teach or suggest evaluating a binding property of a polynucleotide probe. Bao does not teach or suggest using a ratio of the amount of hybridization by a first, specific hybridization sample (containing mostly target) to a polynucleotide probe, and the amount of hybridization by a second, non-specific hybridization sample to the polynucleotide probe as a measure of a binding property of the probe.

Brown teaches methods and apparatuses for forming microarrays of cDNAs on a support. Brown also teaches hybridization of nucleic acid samples to its microarrays. For example, in Example 1 (Brown, column 16, line 3 through column 17, line 40), Brown teaches hybridization to its microarray of two pools of nucleic acids, in which one pool contains random amplification products of the six large yeast chromosomes and the other pool contains random amplification products of the ten small yeast chromosomes. The

hybridization values of spots or clones on the array identify to which of the two pools the clones belong and correlate the clone to the location on the yeast genome (see, e.g., Brown, col. 17, lines 3-40). Brown teaches two-color fluorescence detection of HAT4 gene expression in wild-type Arabidopsis and in a clone of transgenic Arabidopsis in which HAT4 gene is present at ten times the level of that in the wild-type Arabidopsis (Brown, column 15, lines 5-18; and column 17, line 42 through column 18, line 30). Brown does not teach or suggest evaluating a binding property of a polynucleotide probe. Brown does not teach or suggest using a ratio of the amount of hybridization by a first, specific hybridization sample (containing mostly target) to a polynucleotide probe and the amount of hybridization of by a second, non-specific hybridization sample to the polynucleotide probe as a measure of a binding property of the probe. Brown does not teach or suggest using a deletion mutant in hybridization.

B. <u>The Rejection of Claims 27-30, 33-36, 44-47, 59-68, 73-75, 90, 91 and 93 over Lockhart In View of Bao Is Erroneous and Should Be Reversed</u>

The Examiner contended that "it would have been obvious to one skilled in the art at the time the invention was made to apply the ratio determination taught by Bao and to determine the ratio of the hybridization amounts of the first sample and the second sample" and that "[o]ne of ordinary skill in the art would have been motivated to determine the ratio based on the teaching of Bao et al wherein the ratio between signal and background is the most important information for quality control." (the Final Office Action dated April 7, 2003, page 3 bridging to page 4). Appellant respectfully disagrees.

A finding of obviousness under 35 U.S.C. §103 requires a determination of: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the difference between the claimed subject matter and the prior art; and (4) whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1966).

The relevant inquiry is: (1) whether the prior art suggests the invention; and (2) whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

When selective combination of prior art references is required to render obvious a subsequent invention, "there must be some reason for the combination other than the hindsight gleaned from the invention itself. There must be 'something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132 (Fed. Cir. 1985). "Not only must the claimed invention as a whole be evaluated, but so also must the references as a whole, so that their teachings are applied in the context of their significance to a technician at the time--a technician without our knowledge of the solution." *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132 (Fed. Cir. 1985).

The case law has been especially vigorous on guarding against using "hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention" (see, e.g., *In re Fine*, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988)). The Federal Circuit said in *In re Dembiczak*

> Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is *rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references*. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight.

In re Dembiczak, 175 F.3d 994 (Fed. Cir. 1999) (emphasis added). With respect to what might meet the requirement of a showing of motivation, the Federal Circuit said that

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, *the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed*.

In re Rouffet, 149 F.3d 1350 (Fed. Cir. 1998) (emphasis added). With respect to the sources where motivation to combine may be found, the Federal Circuit stated that "[t]his court has identified three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." (*In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998))

The case law has held that if a reference teaches away from combining with another reference, then there is no suggestion to combine. For example, in *Tec Air, Inc., v. Denso Manufacturing Michigan Inc*, the Federal Circuit held that "[t]here is no suggestion to combine, however, if a reference teaches away from its combination with another source" and that "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant ... [or] if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant" (*Tec Air, Inc., v. Denso Manufacturing Michigan Inc*, 52 U.S.P.Q.2d 1294 (Fed. Cir. 1999)). The Federal Circuit has also held that if a proposed modification would render the prior art apparatus inoperable for its intended purpose, the prior art teaches away from the proposed modification. See, *In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1984).

The case law further held that each reference must be evaluated as a whole, i.e., disclosures in the reference that diverge from and teach away from the invention can not be disregarded. "It is *impermissible* within the framework of a Section 103 rejection *to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the reference fairly suggests* to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238 (C.C.P.A. 1965) (emphasis added). In *Bausch & Lomb, Inc., v. Barnes-Hind*, the Federal Circuit has found that the district court erred in engaging in improper hindsight analysis because

> Barnes-Hind selected a single line out of the Caddell specification to support the above assertion. ... This statement, however, was improperly taken out of context... A full appreciation of Caddell's statement requires consideration of the immediately following sentences in the same paragraph and the paragraph after that. ... The district court improperly viewed an isolated line in Caddell in light of the teaching of the `814 patent to hold for obviousness. This is improper hindsight analysis.

Bausch & Lomb, Inc., v. Barnes-Hind, 796 F.2d 443 (Fed. Cir. 1986).

In the present instance, with respect to the first issue on appeal, the relevant inquiry is whether the prior art, alone or in combination, suggests the presently claimed invention. More specifically, whether the prior art suggests combining Lockhart's probe optimization method, which involves first hybridizing the probes with their target nucleic acid alone and then hybridizing the probes with a high complexity, high concentration nucleic acid sample

that does not contain the targets complementary to the probes, and selecting those probes that show a strong hybridization signal with their target and little or no cross-hybridization with the high complexity sample as preferred probes for use in the high density arrays, with Bao's teaching of determining fluorescence intensity ratio of a tissue mRNA or cDNA sample and a reference sample such that the appealed claims would be rendered obvious.

Appellant respectfully asserts that Lockhart and Bao, alone or in combination, does not render the appealed claims obvious, and that one skilled in the art would not have been motivated to combine the teachings of Lockhart with Bao in a manner so as to render the appealed claims obvious for the following reasons.

First, as discussed above, Appellant respectfully submits that Lockhart does not teach or suggest evaluating the binding property of a probe by comparing *directly* (e.g., via a ratio) the hybridization signal of the probe from a specific hybridization sample (containing mostly target) with the cross-hybridization signal from a non-specific (complex; see Summary of the Invention hereinabove) hybridization sample. As such, Lockhart neither teaches nor suggests the presently claimed invention. Lockhart also does not provide motivation to one of skill in the art to combine Lockhart with Bao. In the Final Office Action dated April 7, 2003, the Examiner first contended that

> Regarding Claim 27, Lockhart et al teach a method for evaluating a binding property of a polynucleotide probe comprising a predetermined nucleotide sequence to a target nucleotide sequence, said method comprising: comparing the amount of hybridization of polynucleotide [sic] in a first sample to the polynucleotide probe and the amount of hybridization of polynucleotides in a second sample to the probe wherein the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence and said second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a sequences [sic] that is different from the nucleotide sequences of other polynucleotide molecules in said plurality of different polynucleotide molecules and wherein at least 75% of the polynucleotides in the first sample are polynucleotides comprising said target nucleotide sequence thereby evaluating said binding property of said probe (Column 36, lines 24-47 and Example 1, Column 70, lines 58-Column 73, line 46).

At the outset, Appellant respectfully points out that what is allegedly taught by Lockhart is in fact the claim language of the rejected claim verbatim minus the limitation of determining a ratio. Appellant respectfully submits that this allegation is erroneous.

As discussed above, Lockhart teaches selection of probes by evaluating the hybridization abilities of probes to the target sample and, independently and separately, evaluating the hybridization abilities of the probes to the non-target sample. Although Lockhart teaches that "[t]hose probes that show a strong hybridization signal with their target and little or no cross-hybridization with the high complexity sample are preferred probes for use in the high density arrays of this invention" (Lockhart, column 36, lines 44-47), this statement does not suggest comparing hybridization signal with their target with hybridization signal with the high complexity sample. This is because, as discussed above, Lockhart teaches utilizing separately hybridization to target in a comparison to a threshold level, and hybridization to the high complexity sample in a comparison to a threshold level. When read in the context of the disclosure of Lockhart, e.g., the paragraphs at column 37, lines 1-41, one of ordinary skill in the art would understand that in Lockhart probes that show a strong hybridization signal with their target are probes whose hybridization signals with their targets are above a threshold value. Appellant respectfully directs the attention of the Board to the paragraph at column 37, lines 1-12, of Lockhart, where Lockhart teaches that

> Only those probes where the difference between the probe and its mismatch control exceeds a threshold hybridization intensity (e.g. preferably greater than 10% of the background signal intensity, more preferably greater than 20% of the background signal intensity and most preferably greater than 50% of the background signal intensity) are selected.

(Lockhart, column 37, lines 5-11).

One of ordinary skill in the art would also understand that in Lockhart probes that show little or no cross-hybridization with the high complexity sample are probes whose cross-hybridization is below a threshold value. Appellant respectfully directs the attention of the Board to the paragraph at column 37, lines 24-41, of Lockhart, where Lockhart teaches that

> Only those probes where both the probe and its mismatch control show hybridization intensities below a threshold value (e.g. less than about 5 times the background signal intensity, preferably equal to or less than about 2 times the background signal intensity, more preferably equal to or less than about 1 times the background signal intensity, and most preferably equal or less than about half background signal intensity) are selected.

(Lockhart, column 37, lines 24-31).

In addition, Lockhart teaches that

> Using the hybridization and cross-hybridization data obtained as described above, graphs can be made of hybridization and cross-hybridization intensities versus various probe properties e.g., number of As, number of Cs in a window of 8 bases, palindomic strength, etc. The graphs can then be examined for correlations between those properties and the hybridization *or* cross-hybridization intensities. Thresholds can be set beyond which it looks like hybridization is always poor *or* cross hybridization is always very strong. If any probe fails *one of the criteria*, it is rejected from the set of probes and therefore, not placed on the chip.

(Lockhart, column 37, lines 44-55) (emphasis added).

From these passages of Lockhart, one of ordinary skill in the art would clearly understand that Lockhart does not suggest direct comparison of the hybridization signal and cross-hybridization signals of each individual probe to evaluate binding properties of the probe, i.e., Lockhart does not teach or suggest combining the hybridization signal and cross-hybridization signal of the same probe into a single quantity, e.g., a ratio, and using such a single quantity as a measure of the binding property of the probe. The Federal Circuit has held in *In re Wesslau* that "[i]t is impermissible within the framework of a Section 103 rejection to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238 (C.C.P.A. 1965). In *Bausch & Lomb, Inc., v. Barnes-Hind*, the Federal Circuit has held that taken a statement out of context to support a 35 U.S.C. § 103 rejection is improper hindsight analysis:

> Barnes-Hind selected a single line out of the Caddell specification to support the above assertion. ... This statement, however, was improperly taken out of context... A full appreciation of Caddell's statement requires consideration of the immediately following sentences in the same paragraph and the paragraph after that. ... The district court improperly viewed an isolated line in Caddell in light of the teaching of the '814 patent to hold for obviousness. This is improper hindsight analysis.

Bausch & Lomb, Inc., v. Barnes-Hind, 796 F.2d 443 (Fed. Cir. 1986). Therefore, Appellant respectfully submit that the Examiner's contention is erroneous.

Thus, in Lockhart, hybridization data of a probe to the target sample and to the high complexity sample are used independently and separately, e.g., for comparison to the respective threshold level. Appellant respectfully points out that a probe which has a high

cross-hybridization with the high complexity sample, i.e., which does not show little or no cross-hybridization with the high complexity sample, may nonetheless exhibit a large ratio between hybridization signal with its target and hybridization signal with the high complexity sample if its hybridization signal with its target is even stronger. Such a probe may be highly desirable for use due to its strong hybridization signal with its target, and is a probe whose binding property can be evaluated according to the instantly claimed invention, but would be excluded from consideration by Lockhart.

The Examiner then contended that one of ordinary skill in the art would have been motivated to combine the teachings of Lockhart with Bao to arrive at the presently claimed invention. In the Final Office Action dated April 7, 2003, the Examiner points to Column 36, lines 24-47, of Lockhart for alleged support for such a contention. The Examiner contended that "Lockhart et al further teach that the amount of hybridization signal from the first and second sample are compared to evaluate binding properties of the probe (Column 36, lines 42). While they do not specifically teach the comparison comprises determining a ratio, their method clearly suggests that the comparison encompasses determining a ratios [sic] because they select probe based on measured comparison and select probes preferably having a signal greater than 50% background (i.e. second sample)." Appellant submits that the contention is also erroneous.

First, Appellant respectfully points out that, contrary to the Examiner's contention, comparison to background level in Lockhart is not comparison to the hybridization level of a probe with the second sample. The background level in Lockhart is not the level of hybridization to the high complexity sample. Background level is generally understood by any one skilled in the art to refer to fluorescence originated from various sources other than the source to be measured. Lockhart's usage of the term is consistent with the conventional usage. For example, background or background signal intensity is explicitly defined in Lockhart, column 9, lines 4-11, as referring to

> hybridization signals resulting from non-specific binding, or other interactions, between the labeled target nucleic acids and components of the oligonucleotide array (e.g., the oligonucleotide probes, control probes, the array substrate, etc.). Background signals may also be produced by intrinsic fluorescence of the array components themselves.

Appellant respectfully points out that the term "non-specific binding" as quoted above in relation to background signal is different from hybridization with a "non-specific" (e.g., the high complexity) sample. An example of such "non-specific binding" is physical adsorption of a labeled nucleic acid molecule to the array surface via, e.g., electrostatic interactions. Such non-specific binding can occur between a nucleic acid molecule and any appropriate molecules and can occur anywhere on the array surface, including areas where no probe exists. Non-specific hybridization of a nucleic acid probe, e.g., hybridization of the probe with a non-specific sample, on the other hand, refers to binding to the probe by a single-stranded nucleic acid molecule through partial base pairing, i.e., binding of the probe to a nucleic acid molecule with one or more mismatches. In fact, in one embodiment of Lockhart, the background is "calculated as the average signal intensity produced by regions of the array *that lack any probes at all*." (Lockhart, column 9, lines 31-33; emphasis added). Thus, Lockhart's background signal is not, and does not suggest, the hybridization signal of the second, high complexity sample.

To further illustrate that Lockhart's background signal is not the hybridization signal of the second, high complexity sample, Appellant respectfully points out that Lockhart teaches comparison to background level in its optional second round of probe selection (Lockhart, Column 37, lines 13-17 and lines 24-33), which involves hybridization with the "second sample," i.e., a nucleic acid sample that is not expected to contain sequences complementary to the probes (Lockhart, Column 37, lines 14-17). In this second round of probe selection, *hybridization with the second sample is compared to the background level*:

> [o]nly those probes where both the probe and its mismatch control show hybridization intensities below a threshold value (e.g. less than about 5 times the background signal intensity, preferably equal to or less than about 2 times the background signal intensity, more preferably equal to or less than about 1 times the background signal intensity, and most preferably equal or less than about half background signal intensity) are selected. In this way probes that show minimal non-specific binding are selected

(Lockhart, Column 37, lines 24-32). As such, Appellant respectfully submits that the Examiner has misunderstood Lockhart regarding this subject matter, and that the Examiner's contention based on such misunderstanding is erroneous.

With respect to the Examiner's contention that Lockhart provides motivation to combine with Bao, because its "method clearly suggests that the comparison encompasses

determining a ratios [sic] because they select probe based on measured comparison and select probes preferably having a signal greater than 50% background (i.e. second sample)," Appellant respectfully submits that the contention is erroneous. Appellant has pointed out above that this contention is erroneous because comparison to background is not comparison to the second, high complexity sample. Appellant further respectfully submits that, irrespective of the error, a mere assertion that Lockhart's method encompasses determining a ratio does not suffice for a showing of suggestion or motivation of using a ratio. In *In re Fine*, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988), the Federal Circuit held that mere assertion that "substitution of one type of detector for another ... would have been within the skill of the art," is not sufficient without "any support for or explanation of this conclusion" (*In re Fine*, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988)). Furthermore, even assuming, *arguendo*, that Lockhart's method does encompass determining a ratio, it establishes at most that the claimed method is a species of Lockhart. It is well established in the case law that disclosure of a generic invention that may encompass a claimed species does not, without more, render the species obvious. In *In re Baird*, the Federal Circuit held that disclosure of generic formula that encompass a claimed compound does not render the claimed compound obvious because "particularly when that disclosure indicates a preference leading away from the claimed compounds" (*In re Baird*, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994)). In the present instance, as discussed above, Lockhart clearly teaches utilizing hybridization signal to the target sample in a comparison to a threshold level, and hybridization signal to the high complexity sample in another, separate, comparison to a threshold level, which "leads away" from the presently claimed method of combining the hybridization signal and cross-hybridization signal of a probe into a single quantity, e.g., a ratio, and using such a single quantity as a measure of the binding property of the probe as required by the instant independent claims.

Appellant also points out that other sections of Lockhart that the Examiner cited in the Final Office Action dated April 7, 2003 also do not teach or suggest presently claimed invention. Specifically, column 37, lines 5-12, of Lockhart teaches comparing the intensity difference between a probe and its mismatch control to the background signal intensity; and column 70, line 58, through column 73, line 46, of Lockhart teaches selection of probes in a two-step process, which is also based on intensity difference between a probe and its mismatch control: "[f]irst, in order to be counted, the difference in intensity between a

probe and its corresponding mismatch probe had to exceed a threshold limit" and "[t]hen, the signal for a particular gene was counted as the average difference (perfect match--mismatch control) for the selected probes for each gene" (Lockhart, column 71, lines 1-6 and lines 15-17, respectively). Thus, comparison to background is to evaluate the difference of perfect match--mismatch control for a probe. Appellant respectfully points out that a probe selection method utilizing the intensity difference between a probe and its mismatch control does not teach or suggest the presently claimed method. As such, Appellant respectfully submits that the Examiner has misunderstood Lockhart regarding this subject matter, and that the Examiner's contention based on such misunderstanding is erroneous.

The Examiner then contended that "[a]dditionally, signal intensity and hybridization ratios were well known in the art at the time the claimed invention was made as taught by Bao et al who teach that the ratio of signal to background is the most important information for quality control." The Examiner pointed to column 16, line 45 to column 17, line 62, especially column 17, lines 25-36, in support of this contention. At the outset, Appellant respectfully submits that the Examiner's statement is confusing in various aspects. First, Bao teaches subtraction of background (see Bao, column 17, lines 16-25) rather than a ratio of the signal to background. Secondly, Bao teaches that the most important information is the ratio of background corrected tissue intensity *over* background corrected reference intensity (see Bao, column 17, lines 34-36; emphasis added). Thirdly, Bao teaches that the reference DNA can be used as an indicator for the efficiency of hybridization, since *this reagent* is preferably provided in a predetermined concentration and *is quality controlled* (see Bao, column 17, lines 32-33; emphasis added) rather than for quality control. Thus, there is no teaching in Bao that "the ratio of signal to background is the most important information for quality control." However, Appellant respectfully submits that nonetheless Bao does not supplement what is missing in Lockhart so as to render the presently claimed invention obvious. There is no motivation in Bao to combine Lockhart with Bao to arrive at the presently claimed invention.

As discussed above, Bao teaches a comparative hybridization of a tissue mRNA or cDNA sample, a tissue chromosomal DNA sample, and at least one reference nucleic acid, to the array. In Bao, the fluorescent ratio of (i) the tissue mRNA/cDNA and the reference, and the fluorescent ratio of (ii) the tissue chromosomal DNA and the reference are

determined. Bao does not teach or suggest evaluating a binding property of a polynucleotide probe. Bao does not teach or suggest using a ratio of the amount of hybridization by a first, specific hybridization sample (containing mostly target) to a polynucleotide probe and the amount of hybridization of by a second, non-specific hybridization sample to the polynucleotide probe as a measure of a binding property of the probe. The reference nucleic acid is chosen to permit assessment of the gene expression state and genomic state of the tissue sample relative to the reference (see Bao, column 6, lines 45-49), not to evaluate a binding property of the probe.

Furthermore, Appellant respectfully points out that Lockhart teaches away from the combination with Bao as suggested by the Examiner because the combination would render Lockhart inoperable for the intended purpose of the manner in which Lockhart achieves probe selection. As discussed above, in Lockhart, hybridization data of a probe to the target sample and to the high complexity sample are used independently and separately, e.g., for comparison to the respective threshold level. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ... would be led in a direction divergent from the path that was taken by the applicant" (*Tec Air, Inc., v. Denso Manufacturing Michigan Inc*, 52 U.S.P.Q.2d 1294 (Fed. Cir. 1999)). Lockhart's methods are also incompatible to using a ratio between hybridization signal to the target sample and cross-hybridization signal to the non-target sample. For example, Lockhart teaches calculating the difference of hybridization signals from perfect match (PM) and mismatch (MM) probes. Such differences cannot be calculated using a ratio of hybridization signals of the PM probe with a specific sample and a non-specific sample and a ratio of hybridization signals of the MM probe with a specific sample and a non-specific sample. Even if assuming, *arguendo*, that the differences of such ratios can be taken, it cannot be used to select "those probes where the difference between the probe and its mismatch control exceeds a threshold hybridization intensity (e.g. preferably greater than 10% of the background signal intensity, more preferably greater than 20% of the background signal intensity and most preferably greater than 50% of the background signal intensity)" (Lockhart, column 37, lines 5-11). Similarly, it is impossible to use a ratio of hybridization signals of the PM probe with a specific sample and a non-specific sample and a ratio of hybridization signals of the MM probe with a specific sample and a non-specific sample to select "probes where both the probe and its mismatch control show hybridization intensities

below a threshold value (e.g. less than about 5 times the background signal intensity, preferably equal to or less than about 2 times the background signal intensity, more preferably equal to or less than about 1 times" (Lockhart, column 37, lines 24-31). Thus, combining Lockhart with Bao in the manner suggested by the Examiner would render Lockhart inoperable for its intended purpose. The Federal Circuit has held that if a proposed modification would render the prior art apparatus inoperable for its intended purpose, the prior art teaches away from the proposed modification. See, *In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1984). Thus, Appellant respectfully submits that because Lockhart teaches away from the modification as suggested by the Examiner, there is no suggestion to combine Lockhart and Bao (see, *Tec Air, Inc., v. Denso Manufacturing Michigan Inc*, 52 U.S.P.Q.2d 1294 (Fed. Cir. 1999)).

Thus, nowhere does Lockhart or Bao teach or suggest combining the hybridization signal and cross-hybridization signal of a probe into a single quantity, e.g., a ratio, and using such a single quantity as a measure of the binding property of the probe as required by the instant independent claims. There is no teaching, suggestion, or motivation in either Lockhart or Bao that its respective method can be combined to produce the presently claimed invention. There is no teaching, suggestion, or motivation in either Lockhart or Bao to combine with the other reference to produce the claimed invention as the Examiner contended. The Federal Circuit has held that there must be "something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132 (Fed. Cir. 1985). The Examiner's alleged combination clearly failed this test.

The Examiner fails to "show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed" *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998). Appellant has discussed above each of the Examiner's contentions, and demonstrated that each of the contentions is erroneous. The Federal Circuit has held that "evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved" (*In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999); see, also, *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998)). In the present instance, the Examiner fails to show evidence of suggestion or

motivation under any one of these sources. Absence of a showing of any objective suggestion or motivation, the Examiner's assertions are nothing more than "[b]road conclusory statements regarding the teaching of multiple references," which, standing alone, "are not 'evidence'" (*In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999)).

Appellant respectfully submits that the combination as contended by the Examiner is clearly a result of "hindsight reconstruction by picking and choosing among isolated disclosures in the prior art to deprecate the claimed invention." The Examiner improperly used the inventor's disclosure as a blueprint, and piecing together isolated disclosures in Lockhart and Bao to defeat the claimed invention. In order to pick and choose in the prior art to arrive at the presently claimed invention, the Examiner failed to use each reference as a whole by either disregarding disclosures in the reference that diverge from and teach away from the invention or by mischaracterizing selected disclosures of the references. The Examiner also fails to evaluate Lockhart and Bao as a whole to a technician without the knowledge of the solution as gleaned from the presently claimed invention.

With respect to the dependent claims, Appellant respectfully submits that because independent claims 27 and 67 are not rendered obvious by Lockhart and/or Bao, the dependent claims are also nonobvious. The Federal Circuit has held that "[d]ependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious." *In re Fine*, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988). Thus, Examiner's rejection of dependent claims 28-30, 33-36, 44-47, 59-66, 68, 73-75, and 90 are also erroneous.

In view of the foregoing, Appellant respectfully submits that Lockhart and Bao, alone or in combination, do not render claims 27-30, 33-36, 44-47, 59-68, 73-75, 90, 91 and 93 obvious. The rejection is in error, and should be reversed.

C. The Rejection of Claims 37-40, 42, 43, 48-54, 84, 85, 90, 92 and 94-104 over Lockhart In View of Bao In Further view of Brown Is Erroneous and Should Be Reversed

With respect to the second issue on appeal , the Examiner contended that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the second sample of Lockhart with the deletion mutant of Brown to thereby analyze and evaluate polynucleotide probes. The Examiner also contended that it would have been

obvious to one of ordinary skill in the art at the time of the invention to modify the first sample of Lockhart by adding molecules not comprising the target sequence as taught by Brown and to analyze cross-hybridization between target-specific probes. Appellant respectfully disagrees.

Appellant respectfully points out that Brown does not teach or suggest the use of a deletion mutant. The sections of Brown cited by the Examiner teaches the use of a wild-type strain of Arabidopsis and a transgenic strain of Arabidopsis that expresses the HAT4 gene at a higher level. Appellant respectfully submits that such a transgenic strain of Arabidopsis that expresses the HAT4 gene at a higher level is *not* a deletion mutant. With respect to the proposed modification of the first sample of Lockhart by adding molecules not comprising the target sequence, Appellant first respectfully points out that Brown does not teach or suggest such a modification. Appellant further respectfully submits that the proposed modification is yet another example of hindsight reconstruction. Lockhart teaches that the probes are hybridized with "their target nucleic acid *alone*" (Lockhart, column 36, lines 33-34; emphasis added). Thus, not only there is no suggestion or motivation in Lockhart to make the proposed modification, but there is clear teaching in Lockhart leading away from the proposed modification. Thus, Examiner not only fails to show any evidence of suggestion or motivation to make the modification, but also commits to "picking and choosing among isolated disclosures in the prior art to deprecate the claimed invention" in such a manner as amounting to a disregard of the teachings in the prior art.

However, Appellant respectfully submits that, nonetheless, the rejection based on Lockhart in view of Bao in further view of Brown is erroneous. As discussed above, the deficiency of Lockhart and Bao rests on the fact that they, alone or in combination, do not teach or suggest evaluating a binding property of a polynucleotide probe using a ratio of the amount of hybridization by a first, specific hybridization sample (containing mostly target), to a polynucleotide probe and the amount of hybridization of by a second, non-specific hybridization sample to the polynucleotide probe as a measure of a binding property of the probe. Brown does not teach or suggest evaluating a binding property of a polynucleotide probe. Brown does not teach or suggest using a ratio of the amount of hybridization by a first, specific hybridization sample, to a polynucleotide probe and the amount of hybridization of by a second, non-specific hybridization sample, to the polynucleotide probe as a measure of a binding property of the probe. The Federal Circuit has held that

"[d]ependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious." *In re Fine*, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988). Thus, irrespective of whether or not Brown teaches a sample comprising a deletion mutant, or modifying Lockhart's first sample by adding molecules not comprising the target sequence, Brown does not supplement what is missing in Lockhart and Bao.

Appellant further respectfully points out that many of the Examiner's particular contentions in the Office Action mailed April 7, 2003 regarding Lockhart or Brown with respect to the dependent claims are factually erroneous, as described below.

With respect to claims 39, 42, 92 and 94, the Examiner contends that "Lockhart et al teach the method wherein the target sequence is a gene transcript and the first sample comprises a sample from a wild-type cell which expressed the gene transcript (Column 36, lines 24-47)" (pages 11 and 14 of the Office Action mailed April 7, 2003, respectively). With respect to claims 48-54 and 100-104, the Examiner contends that "Lockhart et al teach the method wherein the first sample does not contain polynucleotides comprising the target sequence (Column 36, lines 24-47)" (pages 13 and 16 of the Office Action mailed April 7, 2003, respectively). To the contrary, Lockhart teaches hybridization with "target nucleic acid alone" rather than with a sample from a wild-type cell expressing the gene transcript (col. 36, lines 33-34).

With respect to claims 43 and 95, the Examiner contends that

> Lockhart et al teach the method ... wherein the amount of polynucleotides in the first sample comprising the target sequence differs from the amount of polynucleotides in the second sample comprising the target sequence by at least a factor of four i.e. the second sample does not comprise the target sequence (Column 36, lines 24-47)

(pages 12 and 15 of the Office Action mailed April 7, 2003, respectively). With respect to claims 96-99, the Examiner contends that

> Lockhart et al teach the method wherein the amount of polynucleotides in the first sample comprising the target sequence differs from the amount of polynucleotides in the second sample comprising the target sequence by at least a factor of four (Claim 44 [sic]), by at least a factor of eight (Claim 45 [sic]), by at least a factor of 20 (Claim 46 [sic]), and by at least a factor of 100 (Claim 47 [sic]) i.e. the second sample does not comprise the target sequence (Column 36, lines 33-47 [sic])

(pages 15-16 of the Office Action mailed April 7, 2003). To the contrary, Lockhart teaches

the absence of the target nucleic acid in the high complexity sample; in order to have the amount of the target nucleic acid in the first and second samples differ by at least a certain factor, the target nucleic acid must at least be present in both samples.

Appellant respectfully submits that the cited sections of Lockhart or Brown do not teach any one of the above respective contentions of the Examiner. The Examiner's rejection based on such erroneous contentions cannot stand.

Thus, Appellant respectfully submits that Lockhart, Bao and Brown, alone or in combination, do not render the presently claimed invention obvious. The rejection is in error, and should be reversed.

D. Claims 91-104 Are Separately Patentable

Notwithstanding the arguments presented in Sections B and C, *supra*, Appellant respectfully submits that claims 40, 42-54, 90 (to the extent claim 90 depends on claims 40 and 42-54), and 91-104 are also not rendered obvious by Lockhart and Bao for the following reasons.

With respect to claims 91 and 93, Appellant respectfully submits that neither claim 91 nor 93 contains the limitation that at least 75% of the polynucleotide molecules in the first sample are polynucleotide molecules comprising the target nucleotide sequence. Thus, the Examiner's rejection of claims 91 and 93 based on a purported Lockhart method in which at least 75% of the polynucleotide molecules in the first sample are polynucleotide molecules comprising the target nucleotide sequence is on its face erroneous.

Regardless of the above-noted error, Appellant respectfully submits that Lockhart teaches away from the claimed methods of claims 40, 42-54, 90 (in part), and 91-104, because Lockhart teaches that the probes are hybridized with "their target nucleic acid *alone*" (Lockhart, column 36, lines 33-34; emphasis added), whereas in the presently claimed methods of claims 40, 42-54, 90 (in part), and 91-104, the first sample comprises both polynucleotide molecules comprising the target nucleotide sequence and polynucleotide molecules that do not comprise the target nucleotide sequence. In particular, claims 40 and 43 specify that "the first sample further comprises polynucleotide molecules that do not comprise the target nucleotide sequence," and claims 91 and 93 specify that the first sample "comprises a plurality of polynucleotide molecules comprising said target

nucleotide sequence *and* a plurality of polynucleotide molecules that do not comprise the target nucleotide sequence" (emphasis added). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ... would be led in a direction divergent from the path that was taken by the applicant" (*Tec Air, Inc., v. Denso Manufacturing Michigan Inc*, 52 U.S.P.Q.2d 1294 (Fed. Cir. 1999)). Lockhart's teaching clearly leads a person of ordinary skill in the art to a method in which the first sample comprises target nucleic acid molecules only, and away from the presently claimed method in which the first sample comprises both target polynucleotide molecules *and* non-target polynucleotide molecules. Therefore, Appellant respectfully submits that claims 40, 43, 91, and 93, and their dependent claims, are nonobvious, and separately patentable.

With respect to dependent claims 42, 44-54 and 90 (to the extent claim 90 depends on claims 40 and 42-54), these claims depend (directly or indirectly) upon claim 43 and thus incorporate the limitation that the first sample contain both polynucleotide molecules comprising the target nucleotide sequence and polynucleotide molecules that do not comprise the target nucleotide sequence. With respect to dependent claims 92 and 94-104, these claims depend upon claim 91 or 93 (directly or indirectly) and thus incorporate the limitation that the first sample contain both polynucleotide molecules comprising the target nucleotide sequence and polynucleotide molecules that do not comprise the target nucleotide sequence. Thus, these claims 42, 44-54, 90 (in part), 92, and 94-104 are nonobvious, and separately patentable, for the reasons presented above in this Section D. In particular, as discussed above, the Federal Circuit has held that "[d]ependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious." *In re Fine*, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988). Thus, Examiner's rejection of dependent claims 42, 44-54, 90 (in part), 92 and 94-104 is also erroneous, and these claims are also separately patentable.

Thus, for the reasons described hereinabove, all of claims 40, 42-54, 90 (to the extent claim 90 depends on claims 40 and 42-54), and 91-104 are separately patentable from claims 27-30, 33-39, 59-68, 73-75, 84-85, and 90 (in part).

E. The Examiner's Assertion in the Advisory Action Mailed September 8, 2003 is Incorrect

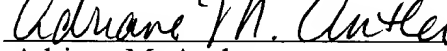
Appellant respectfully submits that the Examiner's assertion in the Advisory Action mailed September 8, 2003 that Appellant "agrees that Lockhart evaluates probe hybridization ability by comparing the hybridization signal between a target sample and the probes to the hybridization signal between a non-target sample and the probe" (see Advisory Action, page 2) is incorrect. Appellant has never agreed to such. Appellant has consistently maintained that Lockhart does not teach or suggest comparing the hybridization signal and the cross-hybridization signal of the same probe directly.

IX. CONCLUSION

For all of the reasons set forth above, Appellant respectfully requests that all of the rejections of the claims on appeal be reversed.

Respectfully submitted,

Date: January 6, 2004



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APPENDIX A
CLAIMS UNDER APPEAL
U.S. APPLICATION NO. 09/616,849
ATTORNEY DOCKET NO. 9301-044

27. (Previously Presented) A method for evaluating a binding property of a polynucleotide probe comprising a predetermined nucleotide sequence to a target nucleotide sequence, said method comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to the polynucleotide probe and the amount of hybridization of polynucleotides in a second sample to the polynucleotide probe, wherein:

(a) the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence; and

(b) the second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a sequence that is different from the nucleotide sequences of any other polynucleotide molecules in said plurality of different polynucleotide molecules,

wherein at least 75% of the polynucleotide molecules in said first sample are polynucleotide molecules comprising said target nucleotide sequence, and wherein said ratio is used as a measure of said binding property, thereby evaluating said binding property of said polynucleotide probe.

28. (Previously Presented) The method of claim 27 wherein the predetermined nucleotide sequence of the polynucleotide probe is complementary to at least a hybridizable portion of the target nucleotide sequence in the first sample.

29. (Previously Presented) The method of claim 27 wherein the target polynucleotide sequence in the first sample is a nucleotide sequence of a gene or gene transcript of a cell or organism, or of an mRNA, cDNA or cRNA derived therefrom.

30. (Previously Presented) The method of claim 27 wherein the plurality of different polynucleotide molecules in the second sample comprise nucleotide sequences of a plurality of genes or gene transcripts of a cell or organism.

33. (Previously Presented) The method of claim 27 wherein at least 90% of the polynucleotide molecules in said first sample are said polynucleotide molecules comprising said target nucleotide sequence.

34. (Previously Presented) The method of claim 33 wherein at least 95% of the polynucleotide molecules in said first sample are said polynucleotide molecules comprising said target nucleotide sequence.

35. (Previously Presented) The method of claim 34 wherein at least 99% of the polynucleotide molecules in said first sample are said polynucleotide molecules comprising said target nucleotide sequence.

36. (Previously Presented) The method of claim 27 wherein each different polynucleotide molecule in the second sample does not comprise the target nucleotide sequence.

37. (Previously Presented) The method of claim 36 wherein:

(a) the target polynucleotide sequence in the first sample is a sequence of a gene or gene transcript of a cell or organism; and

(b) the second sample comprises a polynucleotide sample from a deletion mutant of the cell or organism,

wherein the deletion mutant of the cell or organism does not express the gene or gene transcript.

38. (Previously Presented) The method of claim 27 wherein the plurality of different polynucleotide molecules in the second sample comprises:

(a) polynucleotide molecules comprising the target nucleotide sequence, and

(b) a plurality of different polynucleotide molecules, each comprising a different nucleotide sequence and each not comprising the target nucleotide sequence.

39. (Previously Presented) The method of claim 38 wherein:

(a) the target nucleotide sequence comprises a sequence of a gene or gene transcript of a cell or organism; and

(b) the second sample comprises a polynucleotide sample from a wild-type strain of the cell or organism,

wherein the wild-type strain of the cell or organism expresses the gene or gene transcript.

40. (Previously Presented) The method of claim 27 wherein:

(a) the first sample further comprises polynucleotide molecules that do not comprise the target nucleotide sequence; and

(b) the second sample lacks said polynucleotide molecules comprising said target nucleotide sequence.

42. (Previously Presented) The method of claim 40 wherein:

(a) the target nucleotide sequence is a sequence of a gene or gene transcript of a cell or organism;

(b) the first sample comprises a polynucleotide sample from a wild-type strain of the cell or organism which expresses the gene or gene transcript; and

(c) the second sample comprises a polynucleotide sample from a deletion mutant of the cell or organism which does not express the gene or gene transcript.

43. (Previously Presented) The method of claim 27 wherein

(a) the first sample further comprises polynucleotide molecules that do not comprise the target nucleotide sequence; and

(b) the second sample comprises:

(i) polynucleotide molecules comprising the target nucleotide sequence, and

(ii) a plurality of different polynucleotide molecules, each different polynucleotide molecule comprising a different nucleotide sequence and not comprising the target nucleotide sequence,

wherein the amount of polynucleotide molecules in the first sample comprising the target nucleotide sequence differs by at least a factor of two from the amount of polynucleotide molecules in the second sample comprising the target nucleotide sequence.

44. (Previously Presented) The method of claim 43 wherein the amount of polynucleotide molecules in the first sample comprising the target nucleotide sequence differs from the amount of polynucleotide molecules in the second sample comprising the target nucleotide sequence by at least a factor of four.

45. (Previously Presented) The method of claim 43 wherein the amount of polynucleotide molecules in the first sample comprising the target nucleotide sequence differs from the amount of polynucleotide molecules in the second sample comprising the target nucleotide sequence by at least a factor of eight.

46. (Previously Presented) The method of claim 43 wherein the amount of polynucleotide molecules in the first sample comprising the target nucleotide sequence differs from the amount of polynucleotide molecules in the second sample comprising the target nucleotide sequence by at least a factor of twenty.

47. (Previously Presented) The method of claim 43 wherein the amount of polynucleotide molecules in the first sample comprising the target nucleotide sequence differs from the amount of polynucleotide molecules in the second sample comprising the target nucleotide sequence by at least a factor of 100.

48. (Previously Presented) The method of claim 43 wherein each said polynucleotide molecule that does not comprise the target nucleotide sequence in the first sample is present in the second sample in an amount that differs from the amount of said polynucleotide molecule in the first sample by no more than a factor of 100.

49. (Previously Presented) The method of claim 43 wherein each said polynucleotide molecule that does not comprise the target nucleotide sequence in the first sample is present in the second sample in an amount that differs from the amount of said polynucleotide molecule in the first sample by no more than a factor of 10.

50. (Previously Presented) The method of claim 43 wherein each said polynucleotide molecule that does not comprise the target nucleotide sequence in the first sample is present in the second sample in an amount that differs from the amount of said polynucleotide molecule in the first sample by no more than 50%.

51. (Previously Presented) The method of claim 43 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than a factor of two.

52. (Previously Presented) The method of claim 43 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 50%.

53. (Previously Presented) The method of claim 43 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 10%.

54. (Previously Presented) The method of claim 43 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 1%.

59. (Previously Presented) The method of claim 27 wherein the polynucleotide molecules in the first sample are detectably labeled.

60. (Original) The method of claim 27 wherein the polynucleotide molecules in the second sample are detectably labeled.

61. (Original) The method of claim 59 or 60 wherein the polynucleotide molecules are labeled with a fluorescent molecule.

62. (Previously Presented) The method of claim 27 wherein:

(a) the polynucleotide molecules in the first sample are labeled with a first label; and

(b) the polynucleotide molecules in the second sample are labeled with a second label,

the first label being distinguishable from the second label.

63. (Original) The method of claim 62 wherein:

the first label is a first fluorescent molecule, and

the second label is a second fluorescent molecule.

64. (Original) The method of claim 27 wherein the polynucleotide probe is attached to a surface of a support.

65. (Original) The method of claim 27 wherein the polynucleotide probe is one of a plurality of polynucleotide probes.

66. (Previously Presented) The method of claim 65 wherein the plurality of polynucleotide probes comprises polynucleotide probes in an array of polynucleotide probes,

said array having a support with at least one surface and different polynucleotide probes attached to said surface,

wherein each of said different polynucleotide probes attached to said surface is attached to the surface of the support in a different location.

67. (Previously Presented) A method for evaluating a binding property of a plurality of polynucleotide probes to a target nucleotide sequence wherein each polynucleotide probe in the plurality of polynucleotide probes comprises a predetermined nucleotide sequence,

said method comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to each polynucleotide probe in the plurality of polynucleotide probes and the amount of hybridization of polynucleotides in a second sample to each polynucleotide probe in the plurality of polynucleotide probes, wherein:

(a) the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence; and

(b) the second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a nucleotide sequence that is different from nucleotide sequence of any other polynucleotide molecules in said plurality of different polynucleotide molecules,

wherein at least 75% of the polynucleotide molecules in said first sample are polynucleotide molecules comprising said target nucleotide sequence, and wherein said ratio is used as a measure of said binding property, thereby evaluating said binding property of each said polynucleotide probe.

68. (Previously Presented) The method of claim 67 wherein the predetermined nucleotide sequence of each polynucleotide probe is complementary to at least a hybridizable portion of the target nucleotide sequence.

73. (Original) The method of claim 67 wherein each polynucleotide probe in the plurality of polynucleotide probes is attached to a surface of a support.

74. (Previously Presented) The method of claim 67 wherein the plurality of polynucleotide probes comprises polynucleotide probes in an array of probes,

said array having a support with at least one surface and different polynucleotide probes attached to said surface,

wherein each of said different polynucleotide probes attached to said surface in the plurality of probes is attached to the surface of the support in a different location.

75. (Previously Presented) The method of claim 67 wherein the first sample comprises two or more different polynucleotide molecules

wherein none of the two or more different polynucleotide molecules hybridizes or cross-hybridizes to a probe that also hybridizes or cross-hybridizes to another one of the two or more different polynucleotide molecules.

84. (Original) The method of claim 27 wherein:

polynucleotides in the first sample are labeled with a first label and polynucleotides in the second sample are labeled with a second label that is distinguishable from the first label;

and further comprising, prior to said step of comparing the steps of:

(i) concurrently contacting the polynucleotide probe with the first sample and the second sample under conditions conducive to hybridization, and

(ii) detecting any binding that occurs between the polynucleotide probe and polynucleotides in the first sample and the second sample.

85. (Previously Presented) The method of claim 84 wherein the second sample lacks polynucleotide molecules of said first sample.

90. (Previously Presented) The method of any one of claims 27-30, 33-40, 42-54, 61-68, 73-75 and 84-85, wherein said polynucleotide molecules comprising said target nucleotide sequence are the same polynucleotide molecule.

91. (Previously Presented) A method for evaluating a binding property of a plurality of polynucleotide probes to a target nucleotide sequence, said method comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to each polynucleotide probe in the plurality of polynucleotide probes and the amount of

hybridization of polynucleotides in a second sample to each polynucleotide probe in the plurality of polynucleotide probes, wherein:

(a) said first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence and a plurality of polynucleotide molecules that do not comprise the target nucleotide sequence; and

(b) said second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a sequence that is different from the nucleotide sequence of any other polynucleotide molecule in said plurality of different polynucleotide molecules, and wherein each different polynucleotide molecule in the second sample does not comprise the target nucleotide sequence

wherein each polynucleotide probe in the plurality of polynucleotide probes comprises a predetermined nucleotide sequence and wherein said ratio is used as a measure of said binding property, thereby evaluating said binding property of said plurality of polynucleotide probes.

92. (Previously Presented) The method of claim 91 wherein:

(a) said target nucleotide sequence is a sequence of a gene or gene transcript of a cell or organism;

(b) said first sample comprises a polynucleotide sample from a wild-type strain of the cell or organism which expresses the gene or gene transcript; and

(c) said second sample comprises a polynucleotide sample from a deletion mutant of the cell or organism that does not express the gene or gene transcript.

93. (Previously Presented) A method for evaluating a binding property of a plurality of polynucleotide probes to a target nucleotide sequence, said method comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to each polynucleotide probe in the plurality of polynucleotide probes and the amount of hybridization of polynucleotides in a second sample to each polynucleotide probe in the plurality of polynucleotide probes, wherein:

(a) said first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence and a plurality of polynucleotide molecules that do not comprise the target nucleotide sequence; and

(b) said second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a sequence that is different from the nucleotide sequence of any other polynucleotide molecule in said plurality of different polynucleotide molecules,

wherein each polynucleotide probe in the plurality of polynucleotide probes comprises a predetermined nucleotide sequence and wherein said ratio is used as a measure of said binding property, thereby comparing said binding property of said plurality of polynucleotide probes.

94. (Previously Presented) The method of claim 93 wherein:

(a) said target nucleotide sequence comprises a sequence of a gene or gene transcript of a cell or organism; and

(b) said second sample comprises a polynucleotide sample from a wild-type strain of said cell or organism, wherein the wild-type strain of the cell or organism expresses the gene or gene transcript.

95. (Previously Presented) The method of claim 93, wherein said second sample comprises:

(b1) polynucleotide molecules comprising the target nucleotide sequence, and

(b2) a plurality of different polynucleotide molecules, each different polynucleotide molecule comprising a different nucleotide sequence and not comprising the target nucleotide sequence,

and wherein the amount of polynucleotide molecules in said first sample comprising the target nucleotide sequence differs by at least a factor of two from the amount of polynucleotide molecules in said second sample comprising the target nucleotide sequence.

96. (Previously Presented) The method of claim 95 wherein the amount of polynucleotide molecules in said first sample comprising said target nucleotide sequence differs from the amount of polynucleotide molecules in said second sample comprising said target nucleotide sequence by at least a factor of four.

97. (Previously Presented) The method of claim 95 wherein the amount of polynucleotide molecules in said first sample comprising said target nucleotide sequence differs from the amount of polynucleotide molecules in said second sample comprising said target nucleotide sequence by at least a factor of eight.

98. (Previously Presented) The method of claim 95 wherein the amount of polynucleotide molecules in said first sample comprising said target nucleotide sequence

differs from the amount of polynucleotide molecules in said second sample comprising said target nucleotide sequence by at least a factor of twenty.

99. (Previously Presented) The method of claim 95 wherein the amount of polynucleotide molecules in said first sample comprising said target nucleotide sequence differs from the amount of polynucleotide molecules in said second sample comprising said target nucleotide sequence by at least a factor of 100.

100. (Previously Presented) The method of claim 95 wherein each said polynucleotide molecule that does not comprise said target nucleotide sequence in said first sample is present in said second sample in an amount that differs from the amount of said polynucleotide molecule in the first sample by no more than 50%.

101. (Previously Presented) The method of claim 95 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than a factor of two.

102. (Previously Presented) The method of claim 95 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 50%.

103. (Previously Presented) The method of claim 95 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do

not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 10%.

104. (Previously Presented) The method of claim 95 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 1%.